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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,099	03/02/2001	A. Michael Frace	98,506-C	1471

23859 7590 04/20/2004

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,099	FRACE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-84 and 90-101* is/are pending in the application.

4a) Of the above claim(s) *24-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 24-84, and 90-94 are pending in the application. In the prior action, mailed on September 25, 2003, claims 90-94 were under consideration and rejected, and claims 24-84 were withdrawn as to non-elected inventions. In the Response filed on January 30, 2004, the Applicant amended claims 90, 91, and 93, and added new claims 95-101. Claims 90-101 are currently pending and under consideration in the application.

Priority

2. **(Prior Objection to claim for priority-maintained)** It was noted in the prior action that the present application lacked the requisite reference to the copending application as required under 37 CFR 1.78(a)(2) and (a)(5). In Response, the Applicant amended the specification to include such reference. However, the amendment was made after the latest of 4 months from the filing date of the present application, or 16 months from the filing date of the copending application. Accordingly, under 37 CFR 1.78(a)(3), the Applicant is not entitled to the benefit for this priority date without filing a Petition for Unintentionally Delayed Claim of Priority. The Applicant has therefore not met the requirements for being afforded the benefit of priority to application 08/906,930.

3. It is further noted that the Applicant has indicated in the amendment to the specification that the present application is a continuation of application 08/906,930. This does not appear to be accurate. This application repeats a substantial portion of prior Application No. 08/906,930,

but it also appears to add and claim additional subject matter not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Examiner Query

4. In the prior action, confirmation that the Applicant is defining the term "transmembrane region" as consisting of residues 26-43 was requested. In the Response, the Applicant stated that "applicants teach a deletion of a significant portion of the transmembrane region that retains amino acid 25..." Further, the Applicant offered the amendment of claim 90 to read on a M2 protein where amino acids 26-43 of the transmembrane region have been deleted. In view of the remarks by the Applicant, the amendment of claim 90, and the fact that claim 93 still refers to the transmembrane region generally, the term "transmembrane region" as it is used in the present application is interpreted as generally applied in the art; i.e. the term is interpreted as including residues 25-43 of the M2 protein.

Claim Objections

5. (Prior Objection- Withdrawn) Claim 93 was objected to for using an improper format as an independent claim. In view of the amendment of the claims, the objection is withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **(Prior Rejection-Withdrawn)** Claims 90-94 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims were rejected because it was unclear what the term "preparing" is intended to convey. In view of Applicant's statements that the term "preparing" is intended to be synonymous with the term "producing," the rejection is withdrawn.

8. **(Prior Rejection- Withdrawn)** Claims 93 and 94 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment to the claims, the rejection is withdrawn.

9. **(Prior Rejection- Withdrawn)** Claims 90-94 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contained subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims read on methods of raising antibodies to any M2 polypeptide. However, while the Applicant has disclosed the making and use of an M2 polypeptide from the influenza A virus, the Applicant has not disclosed the making and use of the claimed polypeptides from other viruses to make an anti-M2 antibody. In view of the amendment to the claims limiting them to embodiments wherein the M2 protein is the influenza M2 protein, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. **(Prior Rejection- Maintained)** Claims 90, 91, and 93 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal et al. (U.S. Patent 5,290,686) in view of Black et al. (J Gen Virol- 74: 1673-77- of record in the IDS), Spaete (U.S. Patent 5,474,914). The claims read on methods of producing monoclonal antibodies to the M2 protein of the influenza virus comprising the administration to a subject a modified M2 polypeptide, wherein the transmembrane domain of the M2 protein has been deleted from the polypeptide, and a pharmaceutical carrier. The polypeptides may also comprise a substitution of the transmembrane region for one or more neutral or hydrophilic amino residues. The Applicant traverses the rejection on the grounds that there is no motivation in the art to make the modified M2 polypeptides of the claimed invention. In particular, the Applicant teaches that the Black and Kendal references are inconsistent with respect to the toxicity problem, and therefore provide no motivation to modify the proteins on that basis, and that the Spaete reference teaches only the modification of another polypeptide with no suggestion that the modification may be applied generally. These arguments are not found persuasive. The rejection is therefore maintained with respect to claims 90, 91, and 93, and extended to new claims 95, 96, and 98.

The teachings of the Kendal, Black, and Spaete references were described in the prior action. Applicant's reading of Black and Kendal appear to be correct with respect to the toxicity

of the protein. However, the Examiner does not agree that the Spaete reference does not suggest the removal of the transmembrane domain of proteins other than CMVgh. The applicant argues that "Spaete only teaches or suggests a particular motivation (escort function) to remove the transmembrane domain of CMVgh, this cannot be properly extrapolated to other proteins for which a different motivation is relevant." The Applicant concludes that, because the motivation to modify in Spaete does not apply to the M2 protein, and because the Kendal and Black references do not provide adequate motivation to remove the transmembrane region of the M2 protein, the rejection must fall.

However, the Applicant has not provided any support for the assertion that the teachings of Spaete providing one motivation for the modification of a protein "cannot be properly extrapolated to other proteins for which a different motivation is relevant." Further, this statement appears to be contrary to statements made by the CCPA and the Federal Circuit. See, MPEP 2144 (sections entitled "Rationale Different From Applicant's is Permissible," quoting and citing the cases of In re Linter, 173 U.S.P.Q. 560 (CCPA 1972), and In re Dillon, 16 U.S.P.Q.2d 1897 (Fed Cir 1990), each holding that the motivation to combine art in an obviousness rejection need not be the same as used by the Applicant so long as the result of the combination would have the properties of the claimed invention). Thus, the fact that the motivation applied by Spaete is other than that applied by the Applicant does not overcome the rejection so long as the Spaete reference is properly applied against the claimed invention.

The Examiner is also not persuaded the fact that Spaete teaches the deletion of the transmembrane region of a protein other than the M2 protein removes the reference as a relevant reference for use in the present rejection. The Applicant's argument with reference to Spaete

appears to be that the reference is Non-analogous art, and therefore cannot be properly applied against the claimed invention. Analogous art "must either be in the field of applicant's endeavor or, if not, then be reasonably " in this case the isolation of a viral protein comprising a hydrophobic region, or art that is reasonably pertinent to the particular problem with which the inventor is concerned." In re Oetiker, 24 USPQ2d 1443, 1445 (Fed Cir 1992). References are considered reasonable pertinent if the substance of the reference "would have commended itself to an inventor's attention in considering his problem." In re Clay, 23 USPQ2d 1058, 1060-61 (Fed Cir 1992). In the present case, the Applicant is concerned with the improved production and isolation of a viral protein from a host cell, wherein the improvement is made through the reduction of the hydrophobicity of the protein. See, Application, page 2. Because Spaete is also concerned with the improvement of the production and isolation of viral proteins by reducing the hydrophobicity of the protein (i.e. deletion of the hydrophobic transmembrane region of the protein), the teachings of this reference are clearly relevant to the present invention. Further, although the teachings of Spaete are directed to the production and isolation of the CMVgh protein, those in the art would have recognized that the teachings regarding the deletion of the hydrophobic transmembrane region of the protein would have also been applicable to the production of other proteins. Thus, Spaete, in teaching the deletion of the CMVgh transmembrane region to increase the ease of protein isolation, provides a motivation for those in the art to perform similar modifications to the M2 proteins. Further, because each of Kendal and Spaete teach the use of the baculovirus expression systems for the production of the respective proteins, those in the art would have had a reasonable expectation of success in the modification of the M2 protein to achieve similar results.

In the Response, the Applicant also added new claims 95, 96, and 98. Of these claims, claim 95 further requires the collection of the antibody produced by the claimed method from the subject. The teachings of Kendal were described in the prior action. The reference further teaches that the recombinant proteins may be used to screen serum samples (thus the collection of serum samples" for the presence of antibodies to the M2 protein. Col. 8, lines 55-68. Because the reference teaches the removal of antibody containing samples from a subject who had been administered M2 protein, the reference teaches the collection of such antibodies from the subject. Thus, claim 95 is also rendered obvious by the indicated references.

Claims 96 and 98 limit the claimed methods to embodiments wherein the antibody is produced through the administration of M2 proteins wherein the transmembrane region alone, or where residues 26-43 of the transmembrane region, have been deleted. Spaete teaches the removal of "all or part" of the transmembrane region. Columns 5-6. Thus, it would have been obvious to those in the art to remove either all, or any portion of the region sufficient to prevent the region from binding with the cell membrane. Because those in the art would immediately have recognized that the removal of all but a single residue of the transmembrane region would be likely to also prevent transmembrane binding, the reference, in combination with the teachings of Kendal and Black, would have rendered obvious the deletion of either the entire, or the region of residues 26-43 from the M2 protein.

Because the Applicant's arguments that there is insufficient motivation to combine the references is not found persuasive for the reasons indicated above, the rejection is maintained with respect to claims 90, 91, and 93, and extended to new claims 95, 96, and 98.

12. **(Prior Rejection- Maintained)** Claims 90- 93 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal in view of Black and Spaete as applied to claim 90 above, and further in view of Anderson et al. (U.S. Patent 6,180,343). Claim 92 further limits the M2 polypeptide described above to embodiments wherein "all of the deleted amino acids are replaced with from one to six glycine residues." The Applicant traverses the rejection on the basis that Anderson does not make up for the alleged deficiencies of the Kendal, Black, Spaete rejection, and that the Anderson reference teaches the use of the glycine linkers to join fusion proteins, and not to substitute deleted residues from within a protein. The traversal is not found persuasive.

The Applicant first argues that Anderson does not "fill in the motivation gap that exists in the other cited art." Because the Examiner is not persuaded that there is such a motivation gap for the reasons discussed above, this traversal is not found persuasive.

The Applicant's second argument is also not found persuasive. As indicated in the prior action, Spaete teaches in column 6 that the deleted residues of the transmembrane region may be substituted with other residues, including hydrophilic residues. As noted by the Applicant, Anderson describes the use of serine-glycine linkers to join proteins in a fusion protein, rather than as substitutuents for deleted residues. However, as the linkers comprise non-hydrophobic residues, and as the linkers are suggested as useful for joining sequences with little interference with the proteins' native function/configuration (Anderson, col. 15), it would have been obvious to those in the art that such linkers would be useful for the connection of the two parts of the protein with the deleted transmembrane region. From the cumulative teachings of the references,

it would have been obvious to those in the art to use linkers such as those suggested by Anderson for the joining of the sequences previously joined by the transmembrane region.

In view of the addition of new claim 101, which reads on similar subject matter to that of claim 92, the rejection is extended to this claim as well. Thus, both claims 92 and 101 are rejected over the teachings of Kendal in view of Black and Spaete, and further in view of Anderson.

13. **(Prior Rejection- Maintained)** Claim 94 was rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal in view of Black, Spaete, and Anderson as applied to claims 90-93 above, and further in view of Ito et al. (J Virol 65: 5491-98- of record in the IDS). Claim 94 further limits method of claim 93 to embodiments wherein the M2 polypeptide is derived from the native M2 protein of the influenza virus strain A/Aichi/2/68 (H3N2). The Applicant traverses this rejection on the same grounds as discussed with reference to the rejection over Kendal in view of Black, Spaete, and Anderson as described above. The rejection is therefore maintained for the reasons indicated above.

14. **(New Rejection-Necessitated by Amendment)** Claims 95, 97, and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal in view of Black and Spaete as applied to claims 90, 91, and 93 above, and further in view of Kaplakis-Deliyannis et al., (Electrophoresis 14: 926-936), and Slepushkin et al., (Vaccine 13(15): 1399-1402- of record in the April 2000 IDS). Claims 97 and 99 further limit the claimed method to embodiments wherein the deletion

region of the M2 protein comprises both the indicated transmembrane region, and from one to twelve residues on the C-terminus side of the transmembrane region.

The teachings of Kendal, Black, and Spaete have been described above. Kaplakis-Deliyannis teaches that antibodies to recombinantly produced influenza M2 proteins may be used to detect the presence of the protein in infected cells. See e.g., abstract. Thus, it would have been obvious from the teachings of this reference that antibodies produced by the method described in the Kendal, Black, and Spaete references could be used for the detection of influenza infection of a cell. Thus, the Kaplakis-Deliyannis reference provides motivation for those in the art to produce and isolate anti-influenza M2 antibodies. However, these references do not teach the deletion of the additional C-terminal region of the M2 protein.

Slepushkin provides teachings relating to the regions of the protein that are reactive to anti-influenza M2 antibodies. In particular, the reference teaches that the regions most reactive to antibodies are those in the N-terminal region, and those that are beyond residue 57 of the protein. See, page 1401, right column, and Table 2 (illustrating that the regions of the peptide most reactive with anti-M2 antibodies are those of PM_2-1, PM_2-6-8, and especially PM_2-1, PM_2-7, and P PM_2-8). From these teachings, it would be obvious to those in the art to make a M2 protein that includes the N-terminal residues and the residues corresponding to PM_2-6-8 of the M2 protein, and that it is not necessary that the at least 12 residues to the C-terminal end of the protein be present for the production of antibodies, as this region does not appear to be the target of the most abundant M2 antibodies. The teachings of this reference, in combination with the teachings of the other references indicated above, therefore renders obvious the claimed methods wherein

the M2 protein lacks both the transmembrane sequence, and the 0-12 residues on the C-terminal side of that sequence.

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 4/19/04

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